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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,545	01/14/2002	Mahin D. Maines	176/60981 (6-11402-1001)	1814

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,545	MAINES, MAHIN D.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Amendment of June 18, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, of June 18, 2004, to the Final Rejection of this case, mailed July 16, 2003, and the Advisory Action, mailed April 6, 2004, is acknowledged. Claims 1, 3, and 8-12 are pending. Claim 3 is withdrawn. It is acknowledged that applicants have amended Claim 1. Claims 1 and 8-12 are hereby reconsidered.

Claims-Objections

Claims 1 and 8-12 are objected to for reciting non-elected subject matter, i.e. "...introducing into a mammalian cell either biliverdin reductase or..." and/or "wherein the modified cell structure is enhanced cell size, ...polar cell morphology, or a combination thereof".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include, but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary;

and (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing cell size and inducing polar cell morphology by introducing into the cell a polynucleotide encoding biliverdin reductase, does not reasonably provide enablement for inducing actin spike formation by introducing into the cell a polynucleotide encoding biliverdin reductase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 8-12 are so broad as to encompass methods for modifying cell structure, including induction of actin spike formation, by introducing into the cell a polynucleotide encoding a biliverdin reductase, wherein the polynucleotide is homologous to SEQ ID NO: 2. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regards to a method of inducing actin spike formation in a cell by introducing into the cell said polynucleotide. The specification discloses that introducing into HeLa cells the polynucleotide of SEQ ID NO: 2, which encodes a biliverdin reductase, induces the formation of spikes on the surface of the cells (Fig 3). However, the disclosure fails to provide working examples for the formation of actin microspikes. Furthermore, the prior art teaches that the spikes observed in Figure 3 are predicted not to be actin microspikes for the following reasons.

Bilirubin is the product of reduction of biliverin by biliverdin reductase. Thus, a person of ordinary skill in the art would predict that bilirubin would mimic the effect of biliverdin reductase. Leipe et al, 1983 teach that treatment of guinea-pig leucocytes with bilirubin induces the formation of cell-surface microspikes (Fig 2). Said microspikes are not actin microspikes since in the presence of colchicine, an inhibitor of actin rearrangement, bilirubin still induced microspike formation (Leipe et al; pg 508, parg 3). Thus, the results of Leipe et al teach away from a method of inducing *actin* microspikes by introducing into a cell a polynucleotide encoding biliverdin reducase, as recited in the instant application.

As discussed with Applicant's representative, Ted Merkel, on August 9 and 10, 2004, a conclusion that the results of Leipe et al teach away from a method of inducing actin microspikes by introducing into a cell a polynucleotide encoding biliverdin reducase has two caveats. First, said conclusion is dependent on the assumption that the effects of biliverdin reductase are mediated by bilirubin. Second, sufficient biliverdin substrate must be present in the cell for the effects of biliverdin reductase to be mediated by the bilirubin product. Said caveats are addressed by the art, as follows.

The instant application discloses that biliverdin reductase has homology to protein kinases (pg 2, line 11-pg 3, line 2) and the art teaches that biliverdin reductase autophosphorylates (Salim et al, 2001; Figs 1, 2, and 4). Said teachings suggest that the effects of biliverdin reductase on microspike formation may be mediated by the kinase activity of biliverdin reductase and may be independent from any effects of bilirubin. However, the art teaches that the kinase activity of biliverdin reductase is not independent from formation of bilirubin, since generation of bilirubin is dependent on

autophosphorylation of biliverdin reductase (Salim et al; Fig 5). Thus, a person of ordinary skill in the art would believe that, more likely than not, an effect of biliverdin reductase as an autophosphorylating kinase is mediated by the generation of bilirubin.

The instant application discloses that transfection of HeLa cells with a polynucleotide encoding biliverdin reductase results in membrane microspike formation. If the effect of expressing biliverdin reductase on microspike formation is mediated by bilirubin, HeLa cells must be contain biliverdin. Baranano et al teach that biliverdin reductase, by converting endogenous biliverdin to bilirubin, acts a cytoprotectant in HeLa cells (Figs 4 & 5). Thus, a person of ordinary skill in the art would conclude that, more likely than not, in HeLa cells the effect of biliverdin reductase on microspike formation is mediated by bilirubin.

For these reasons, one of skill in the art would predict that the ability of biliverdin reductase to induce microspike formation is mediated by bilirubin and that said microspikes are not actin microspikes. Therefore, Claims 1 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one of skill in the art to make and use a method for inducing actin spike formation by introducing into the cell a polynucleotide encoding biliverdin reductase.

Written Description

Claims 1 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 8-12 are directed to a genus of methods for enhancing cell size, inducing actin microspike formation, and/or inducing polar cell morphology by introducing into the cell a polynucleotide encoding biliverdin reductase. The specification teaches a method for enhancing cell size and inducing polar cell morphology by introducing into the cell a polynucleotide encoding biliverdin reductase. However, the specification fails to describe any species of methods for inducing actin microspike formation by introducing into the cell a polynucleotide encoding biliverdin reductase. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope
AU 1652